REMARKS

Amendments to the Claims

Claims 1, 3-9 and 12-20 are pending in this application.

Claim 2 has been canceled in this response. Claims 10 and 11 have been previously canceled.

Claims 5-7 and 14-20 are withdrawn.

Claims 1 and 3 have been amended to recite a sub-set of the variables.

No new matter has been added.

Claim Rejections – 35 USC § 103

The Examiner maintains the rejection of claims 1-4, 8, 12, and 13 under 35 U.S.C. § 103 as being unpatentable over Carpenter in view of Odake. The Examiner also maintains the rejection of claims 1-4, 8, 9, 12 and 13 as being unpatentable over Carpenter, in view of Odake, and further in view of Portet. Applicants respectfully traverse both rejections.

a. "Simple Substitution" of one MMP inhibitor for another would not yield predictable results.

The Examiner states that the present invention provides a situation where "simple substitution of one known element for another" obtained "predictable results" (Office Action, page 6). She suggests that "One of ordinary skill in the art could have substituted one known MMP (collagenase) inhibitor for another, and the results of the substitution would have been predictable, that is effective conjugation of the MMP inhibitor to a diagnostic moiety for targeting MMP in localized imaging methods" (Office Action, page 6). Applicants respectfully disagree with the Examiner's assessment that all collagenase inhibitors would have been considered interchangeable. As shown in Odake, inhibitors have different efficacy against different collagenases, and are different from another inhibitor (Odake col. 15-18, table 2). Accordingly, one of skill in the art would not blindly substitute a particular collagenase inhibitor taken from assessment of one collagenase, and apply it to a different physiological purpose for

another collagenase as the Examiner has done. For at least this reason, Applicants request that the rejection be withdrawn.

b. One of skill in the art would have no reasonable expectation of success in achieving successful imaging.

The Examiner also suggests arguing that Odake is directed to therapeutic uses is insufficient because the rejection is based on the combination of Odake and Carpenter, and Carpenter discloses diagnostic uses (Office Action, page 9). Applicants respectfully submit that the Examiner's logic fails to consider the teachings of the cited references.

Applicants maintain that the Examiner has improperly attributed the characteristics of the MMP targeting entity of Carpenter to a peptide which has demonstrated a different activity in a different system, *i.e.*, the MMP inhibitor of Odake. The Examiner is not permitted to merely extract from cited references those teachings that support a conclusion of obviousness. Rather, the references *must be considered as a whole*. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983):

> In its consideration of the prior art, however, the district court erred in ...considering the references in less than their entireties, i.e., in disregarding disclosures in the references that diverge from and teach away from the invention at hand. *In re Kuderna,* 426 F.2d 385, 165 USPQ 575 (CCPA 1970).

The Examiner has provided no evidence that one of skill in the art would have any reasonable expectation that a peptide which has shown MMP inhibitory effect *in vitro* would be expected to have MMP targeting ability *in vivo,* or that the affinity or selectivity for MMP would be sufficient for use as a diagnostic. In contrast, Lancelot *et al.* (of record) expressly compared whether the binding affinity *in vitro* (bound to the signal molecule), *in vitro* (not bound to the signal molecule) and *in vivo* would be the same for compound B (*See* Lancelot, page 426). Because Lancelot *et al.* specifically felt the need to test and report on each of these characteristics, a reasoned explanation would be that the authors did not expect these characteristics to be the same. Thus, Applicants are not arguing the references separately, but are instead highlighting the failure of the Examiner to resolve the differences between the inventive

agents and methods and the combined prior art references. That is, the Examiner's rationale is faulty. Accordingly, Applicants request that the rejection be withdrawn.

c. The claims are commensurate in scope with the evidence of unexpected results.

The Examiner disregards the evidence of unexpected results of record stating that "allegations of unexpected results must be commensurate in scope with the claimed invention" (Office Action, page 10). On page 11 of the Office Action, the Examiner asserts that "In the instant case, applicant alleges unexpected results only for compound B/P947 which is a specific peptide coupled to a specific contrast moiety."

Applicants respectfully submit that the claims as currently pending recite a specific peptide. The evidence of record demonstrates that one of skill in the art would have expected to obtain either no MRI signal or only a non-MMP specific signal. This is because:

- the MMP concentration in the targeted atherosclerotic tissue (atheroma plaque) was about 50 nM

- this very weak quantity could normally not have been detected by MRI with the relaxivity level of the compound used in the present invention (about 5mM-1 Gd-1s-1): indeed according to the common knowledge in the MRI field at the time the application was filed, the sensitivity of MRI should not have been able to allow the imaging of a biological target at a concentration of less than about 10μM to 1 mM. That is, the MMP concentration in the targeted atherosclerotic tissue was at least twenty fold less than the amount which could normally be detected.

Furthermore, looking at Odake (Table 2, cols. 15-18), the IC50 dosage for the collagenase inhibitors reported therein were all in the micro-molar range. Thus, it would have been unexpected to obtain reliable data regarding binding and/or inhibition at the MMP concentrations in the nano-molar range as found in atherosclerotic tissue.

Accordingly, because 1) one of skill in the skill in the art would have not expected to detect MMP by MRI at nano-molar ranges, and 2) because looking at the inhibition data provided in Odake, one of skill in the art would not have expected the inhibitors to "work" in nano-molar ranges, Applicants maintain that one of skill in the art would not have expected the

efficacy of the present invention as a diagnostic in view of Carpenter, Odake and Portet. Applicants request that the rejection be withdrawn.

Conclusion

In view of the above remarks, all of the claims are submitted as defining non-obvious, patentable subject matter. Reconsideration of the rejections and allowance of the claims are respectfully requested. Applicant believes the pending application is in condition for allowance.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Susan W. Gorman, Ph.D., Reg. No. 47,604 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a three (3) month extension of time for filing a reply in connection with the present application, and the required fee of $1,110.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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